

## **ANTI-INFLAMMATORY EFFECT OF *NIGELLA SATIVA* OIL ON CHEMORADIATION-INDUCED ORAL MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCERS**

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### **ABSTRACT**

**Objective:** Oral mucositis (OM) is a common treatment-induced toxicity in patients undergoing radiation or chemoradiation for head and neck cancers (HNC). The study aims to evaluate the anti-inflammatory effect of *Nigella sativa* (NS) oil in radiation-or chemoradiation-induced OM in HNC patients.

**Methods:** From Forty HNC patients were randomized to two groups, each of 20 patients. The first group was treated with NS oil mouthwash five times daily, while the second group was treated with the Magic mouthwash and served as a control. All patients received radiotherapy (RT) (60-70 Gy) in 30-35 fractions over 6-7 w with or without chemotherapy. Patients were evaluated once per week to estimate the severity and duration of OM and the salivary levels of IL-6 and TNF- $\alpha$ .

**Results:** 70% of patients were men and the commonest tumor locations were larynx (47.5%) and pharynx (22.5%) classified as stages III or IV. NS oil significantly reduces RTOG grade and OM severity after 3-4 w of RT, attenuates the elevation in salivary IL-6 and TNF- $\alpha$  production after 3-5 w.

**Conclusion:** *Nigella sativa* oil mouthwash have a potential anti-inflammatory activity that may be beneficial in minimizing or preventing radiation-or chemoradiation-induced oral mucositis in patients with head and neck cancer.

**Keywords:** *Nigella sativa* oil, Oral mucositis, Chemoradiation, Head and neck cancer, Pro-inflammatory cytokines

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### **INTRODUCTION**

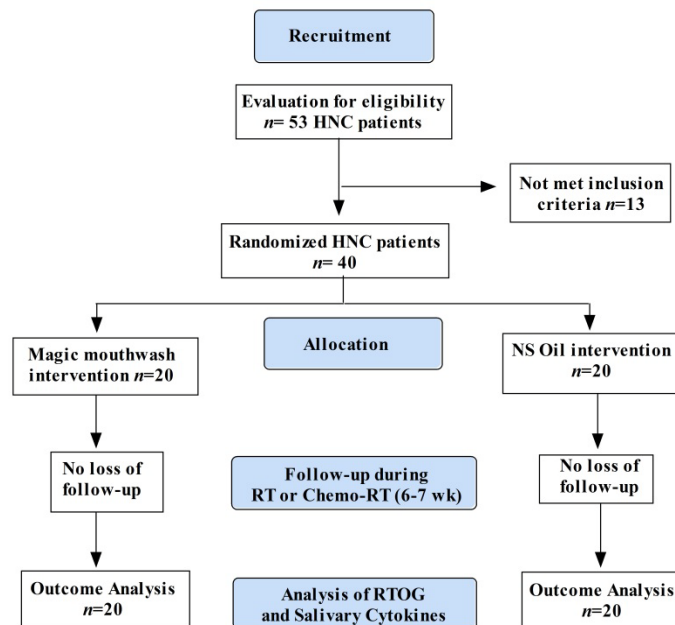
Treatment of patients with head and neck cancers (HNC) with radiotherapy (RT) or chemoradiotherapy induces oral mucositis (OM), a well characterized treatment-induced inflammatory response which is extremely painful and increases the morbidity of those patients [1]. Based on its severity, OM can be ranked as tolerable (grade 1 and 2) and intolerable (grade  $\geq 3$ ) [2]. Radiation or chemoradiation treatment of HNC patients induces tolerable OM in all exposed patients and can be easily managed [3]. However, severe intolerable OM requires special care for the management of pain and facilities to assist for nutritional supplementation [4]. Moreover, severe intolerable OM creates many problems including treatment delay, dose reduction and also termination of the treatment plan with consequent negative impacts on the treatment of the underlying cancers [5]; meanwhile, implantation of extra measures to ameliorate OM increases the possibility of hospitalization time and treatment cost [6]. Currently, the available treatments for OM are mostly palliative and include extensive oral care, use of anti-inflammatory drugs, local anesthetics, antiseptics and antimicrobial agents; meanwhile, no adopted prophylactic or effectively curative agents are available yet for severe intolerable OM [7]. However, the available measures did not show considerable therapeutic benefits and may predispose to many adverse effects for the patients. With respect to the validity of this issue for patients' health status, it is critical to characterize the highly effective approach with the least complications for the prevention and management of severe intolerable OM, which is a vital step toward modifying the severity of this condition. Among the available alternative, the use of natural compounds seems to be rational as a potential approach for ameliorating OM severity. *Nigella sativa* *Ranunculaceae* is characterized as an annual flowering plant and also known as black cummin or a black seed; it is cultivated in several countries in the Mediterranean region, South Europe, Syria, Turkey, and Saudi Arabia

[8]. Ancient physicians utilized the NS seeds in the treatment of several diseases, such as headache and toothache, congestion of the nose, intestinal worms, promotion of menstruation, and production of milk [9]. Many researchers have thoroughly reviewed NS and its active constituents, especially thymoquinone, and reported them to have many therapeutic activities including antimicrobial, anti-inflammatory, analgesic, anti-histamine, antihypertensive, antioxidant and anti-carcinogenic among many others [10, 11]. Moreover, topical application of NS oil was found to have significant therapeutic benefits on the healing of chemically induced oral ulcers and chemotherapy-induced OM in experimental animals [12, 13]. The current pilot study was designed to evaluate the anti-inflammatory activity of NS oil mouthwash and reduction of the incidence of OM in HNC patients undergoing TR or chemoradiotherapy.

### **MATERIALS AND METHODS**

#### **Study design and ethical consideration**

This prospective open-label clinical study was conducted during the period from January 2017 to May 2018. Fifty-three patients of both sexes with ages  $> 18$  y, diagnosed with squamous cell carcinoma of the head and neck, were evaluated at Hiwa Oncology Hospital and Zhyanawa Radiation Center, Sulaimani, Iraq for eligibility. The diagnosis of those patients was histopathologically confirmed and they were scheduled to receive radiotherapy or chemoradiotherapy. Only 40 patients who had a confirmed squamous cell carcinoma of the head and neck and fulfill the required inclusion criteria were enrolled in the study and treated with radiation or chemoradiation (fig. 1). The study protocol was approved by the local Clinical Research Ethics Committee of the College of Medicine, University of Sulaimani (REC-45 in 13/2/2017) in accordance with the updated version of Helsinki declaration and signed informed consent was obtained from all the participants.



**Fig. 1:** Flowchart of the study. HNC, head and neck cancers; NS, *Nigella sativa*; RTOG, radiation therapy oncology group; n, number of patients; RT, radiotherapy

### Inclusion and exclusion criteria

The inclusion criteria include histopathologically confirmed squamous cell carcinoma of the head and neck, primary tumor in the stages T1, T2, T3 or T4, regional node of any N status, distant metastases absent, age 18 y and above, Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1, normal hematologic and biochemical parameters, willingness to fulfill the study requirements and providing a signed consent. Meanwhile, the exclusion criteria include patients with previous surgery in the head and neck, patients undergoing previous radiotherapy, uncontrolled systemic or widely disseminated disease, and presence of a synchronous double primary malignancy or simultaneous participation in another clinical trial.

### Randomization and interventions

It has been estimated that a minimum sample size of 40 patients would enable the detection of clinically significant differences between treatment groups at  $\alpha$  level of 0.05 with a power of 0.80. At the beginning of the study, all the enrolled patients were verified to have no dental problems, mouth ulcers, or mucositis of the oral cavity. All the eligible 40 patients satisfied the inclusion criteria and accepted to participate in the study (fig. 1). The patients were randomly allocated randomized utilizing a block randomization protocol to either magic mouthwash-treated group (control group, 20 patients) or NS oil-treated group (test group, 20 patients). The patients in group A received a topically administered NS oil as mouthwash (BARRY Int. PVT., LTD, Karachi, Pakistan), obtained from a local distributor (Voucher No.: 85-4-2017) and approved for quality assurance by the Department of Pharmaceutics, College of Pharmacy; it has been applied as 10 ml each 6 hr daily starting from the first week after initiation of radiotherapy or radio chemotherapy (60-70 Gy in 30-35 fractions over 6-7 w with or without chemotherapy) up to 6-7 w (the end of the radiation therapy). The patients in control group received a treatment based on the hospital adopted protocol, the "Magic Mouthwash". This formula contains nystatin 100 000 U (Julphar, UAE), tetracycline 0.02% (Triax Pharmaceuticals LLC, USA), lidocaine 0.5% (Pharma Chem Consultech, India), and dexamethasone 0.5% (Pfizer NV, Belgium), which was prepared by expert pharmacist according to a standardized method; the formula was administered as a mouthwash in a similar amount, dosage form and duration as in group A according to the instruction of the medical oncologist.

### Treatment follow-up and outcomes measurement

Based on the in-house adopted protocol, the HNC patients of both groups were treated postoperatively with 30-33 fractions of radiation sessions (60-70 Gy) during 6-7 w (ElectaLinac Synergy, Stockholm, Sweden); meanwhile, some of the enrolled patients received chemotherapy concomitantly with the radiation doses. Whenever chemoradiation was applicable, chemotherapeutic agents were administered according to the local institutional protocol (carboplatin and cetuximab) on a weekly basis 3 h before exposure to the first weekly radiation. On a weekly bases, all participants were evaluated for the occurrence, onset, and severity of OM [1]. Oral mucositis was evaluated before the initiation of RT and at weekly intervals during radiation therapy according to the RTOG (Radiation Therapy Oncology Group) guidelines. The score grades from 0 to 4, indicating progressively more severe degrees of oral mucositis [1]. Scores 1 and 2 were grouped as "tolerable mucositis" and scores 3 and 4 were ranked "intolerable mucositis." Almost all the patients in both groups completed the treatment regimen without dropout from the study; however, a treatment delay occurs in patients who developed OM. Moreover, a sample of saliva was obtained weekly from each patient according to a standardized procedure [14]. Simply, a minimum of 2 ml of unstimulated saliva was collected after oral rinse with water at room temperature. The saliva samples were collected at least three hours after the last meal and the patients were asked to avoid drinking one hour before sampling. Due to the circadian rhythm nature of salivation, samples were collected from 9 to 11 am and immediately frozen at -40 °C. Time points of collection were the same of clinical and biochemical assessment (every week during treatment). Based on Sandwich-ELISA technique, the salivary content of IL-6 and TNF- $\alpha$  were evaluated using a commercial ready-made ELISA kit (Elbscience Biotechnology Inc, Texas, USA).

### Statistical analysis

The results were analyzed utilizing SPSS 10.0 software and GraphPad Prism 6.1 software. The qualitative data are present as simple frequencies and percentages. The nominal data were analyzed using Fisher's exact test and  $\chi^2$  test. The ranking data and some of the quantitative data which didn't show normal distribution clearly (lesion duration and pain severity) were analyzed using Mann Whitney test. Continuous data were analyzed using paired and unpaired *t*-test. Spearman's correlation was utilized to analyze the association between the anti-inflammatory markers and OM severity according to the RTOG score.  $P < 0.05$  was considered for statistical significance.

## RESULTS

The characteristics of the enrolled HNC patients are presented in table 1. No significant differences were observed between the two groups regarding patient or tumor characteristics. All the randomized patients in both groups comply well and completed the RT or chemo-RT schedule and perfectly followed the instruction of using the mouthwash and gargling procedure. Accordingly, all the enrolled and randomized patients were included in the follow-up and outcomes

assessment process. The gender, age and cigarette smoking habits were found similar. Moreover, the parameters of diagnosis and treatment like the location and stage of cancer, the histopathological features that indicate the picture of squamous cell carcinoma were also similar in the 2 groups. The majority of the HNC patients was males (70%) and demonstrated primary locations of the neoplasm as follow: larynx (47.5%); pharynx (22.5%); oral cavity (10%) and the nasopharynx (10%). All of the cancers were newly diagnosed and most of them were ranked as stage III or stage IV.

**Table 1: Demographic characteristics and baseline data of the HNC patients**

Variables	Control n (%)	NS Oil n(%)	P-value
<i>Age (years)</i>			
≤ 65	13(65)	16(80)	
>65	7(35)	4(20)	0.29
<i>Gender</i>			
Female	5(25)	7(35)	
Male	15(75)	13(65)	0.50
<i>Dental status</i>			
Good	3(15)	0(0)	
Fair	2(10)	9(45)	
Bad	10(50)	6(30)	
Edentulous	5(25)	5(25)	0.05
<i>Previous Medical History</i>			
None	5(25)	10(50)	
Comorbidities	15(75)	10(50)	0.10
<i>Tumor Location</i>			
Larynx	10(50)	9(45)	
Nasal cavity	2(10)	2(10)	
Oral cavity	1(5)	3(15)	
Others	1(5)	3(15)	
Pharynx	6(30)	3(15)	0.63
<i>Stage of Cancer</i>			
I	1(5)	4(20)	
II	3(15)	2(20)	
III	8(40)	6(30)	
IV	8(40)	8(40)	0.60
<i>Total Radiation dose</i>			
7000	13(65)	9(45)	
6600	2(10)	6(30)	
6300	5(25)	5(25)	0.26
<i>Number of fractions</i>			
≤ 30	6(30)	7(35)	
33	4(20)	9(45)	
35	10(50)	4(20)	0.10
<i>Type of chemotherapy during RT</i>			
None	8(40)	10(50)	
Carboplatin	2(10)	1(5)	
Cisplatin	7(35)	8(40)	
Cetuximab	3(15)	1(5)	0.73
<i>Interruption of RT</i>			
No	15(75)	16(80)	
Yes	5(25)	4(20)	>0.99
<i>Duration of RT (week)</i>			
Six	6(30)	8(40)	
Seven	14(70)	12(60)	0.51

Values are simple frequency and percentage. NS, *Nigella sativa*; HNC, head and neck cancer; RT, radiotherapy; n, number of patients.

Fig. 2 showed that the incidence and severity of OM according to the RTOG scale were increased with time in both groups; meanwhile, significant differences in the RTOG score were reported at week-3 of treatment in both groups compared with those reported at week-1. However, the NS oil-treated group showed a significantly lower incidence and severity compared with the control group ( $P<0.05$ ) at week-4 and maintained up to the end of treatment. Considering all the treatment period, the area under the curve (AUC) in the NS oil group demonstrates a significantly lower mean value compared with that of the control group (8.34 vs. 14.9;  $P<0.01$ ).

Fig. 3 indicated that the duration of OM within the RTOG scores of 2, 3 and 4 was not significantly different ( $P=0.29$ ) compared with that reported in the control group within the same RTOG scale range.

Similarly, the OM duration (weeks) was not significantly different between the two groups within the RTOG scale range of 2 and 4 ( $P=0.27$ ). However, the duration of OM in both groups within 3 and 4 TOG sores was significantly lower than that reported within the RTOG scores of 2, 3 and 4 ( $P<0.05$ ).

In fig. 4, the salivary IL-6 concentrations were elevated with time during exposure to RT or chemo-RT in both groups; this pattern of elevation reaches the maximum in both groups at week-3 of treatment and declines up to the end of the treatment period. The salivary content at each time point was not significantly different between the two groups through the entire treatment interval ( $P>0.05$ ). However, the AUC in the NS oil group was found to be significantly lower than that reported in the control group (4396 vs. 6204;  $P<0.05$ ).

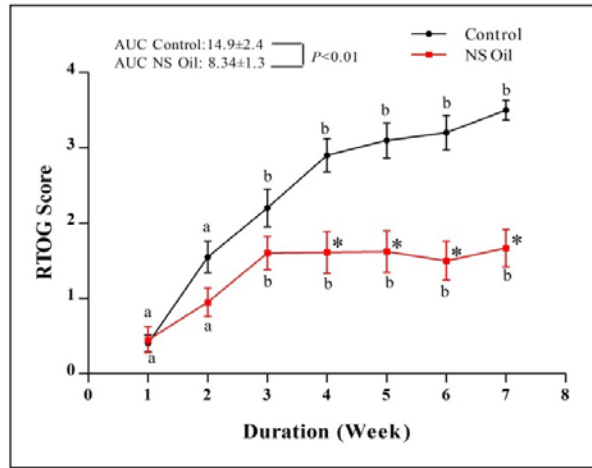


Fig. 2: Effect of NS oil mouthwash on the severity of OM assessed by RTOG in HNC patients exposed to RT or Chemo-RT;  $n=20$  patients in each group; values are mean±SEM; \* significantly different compared with control group within the same period (unpaired  $t$ -test,  $P<0.05$ ); values with different letters (a,b) within the same group are significantly different (ANOVA and Bonferroni's *post hoc* test,  $P<0.05$ ). AUC, area under the curve; NS, *Nigella sativa*; OM, oral mucositis, RT, radiotherapy; RTOG, radiation therapy oncology group; HNC, head and neck cancers

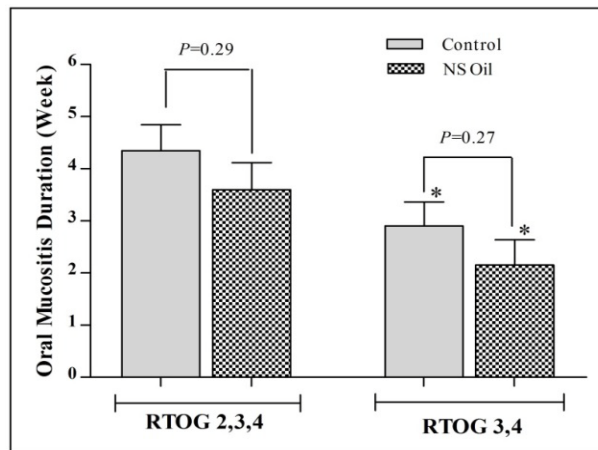


Fig. 3: Effect of NS oil mouthwash on the duration of severe OM assessed by RTOG in HNC patients exposed to RT or Chemo-RT;  $n=20$  patients in each group; values are mean±SEM; \* significantly different within the same group at different severity score (unpaired  $t$ -test,  $P<0.05$ ); comparison between different groups utilized unpaired  $t$ -test. NS, *Nigella sativa*; RTOG, radiation therapy oncology group; RT, OM, oral mucositis; radiotherapy; HNC, head and neck cancers

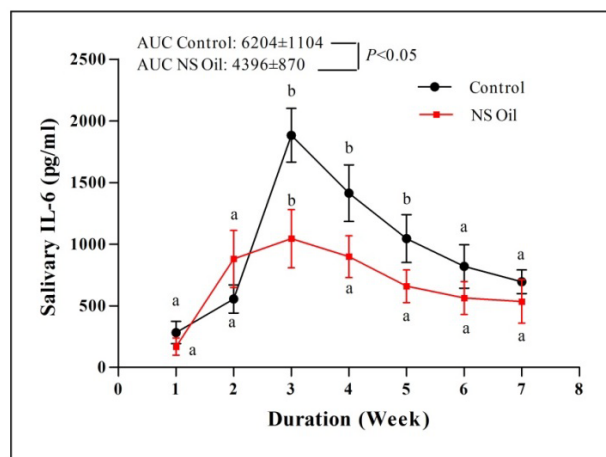
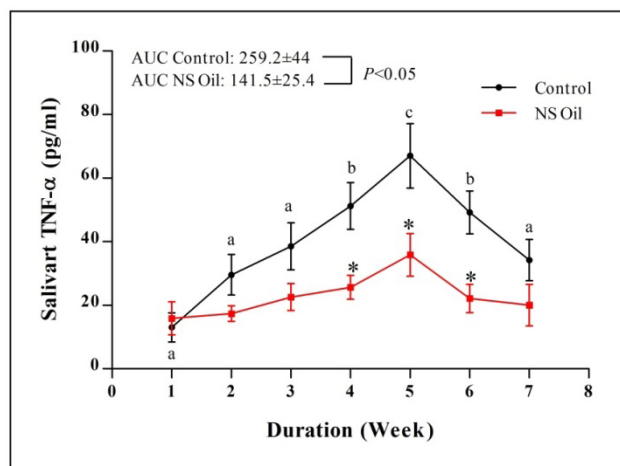


Fig. 4: Effect of NS oil mouthwash on the salivary IL-6 level of HNC patients with RT or Chemo-RT induced OM;  $n=20$  patients in each group; values are mean±SEM; No significant differences between the control group and NS oil group within the same period (unpaired  $t$ -test,  $P>0.05$ ); values with different letters (a,b) within the same group are significantly different (ANOVA and Bonferroni's *post hoc* test,  $P<0.05$ ). AUC, area under the curve; NS, *Nigella sativa*; RT, radiotherapy; OM, oral mucositis; HNC, head, and neck cancers

In fig. 5, the salivary TNF- $\alpha$  concentrations of the control group showed significantly increased levels ( $P<0.05$ ) at week-4, achieved maximum values at week-5 and then started declining significantly up to the end of treatment (week-7). Meanwhile, the salivary TNF- $\alpha$  concentrations of the NS oil-treated group showed a non-significant elevation pattern throughout the entire treatment interval ( $P>0.05$ ) compared with the week-1 of treatment. Additionally, the salivary

TNF- $\alpha$  contents of the NS oil group at the weeks 4, 5 and 6 of the treatment were significantly lower compared with their corresponding values of the control group within the same time points ( $P<0.05$ ). Considering all the changes in salivary TNF- $\alpha$  throughout the entire treatment period, the AUC value of the NS oil group was significantly lower than that of the control group (141 vs. 259.2;  $P<0.05$ ).



**Fig. 5: Effect of NS oil mouthwash on the salivary TNF- $\alpha$  level of HNC patients with RT or Chemo-RT induced OM; n= 20 patients in each group; values are mean $\pm$ SEM; \* significantly different compared with the control group within the same period (unpaired *t*-test,  $P<0.05$ ); values with different letters (a,b,c) within the same group are significantly different (ANOVA and Bonferroni's *post hoc* test,  $P<0.05$ ). AUC, area under the curve; NS, *Nigella sativa*; RT, radiotherapy; OM, oral mucositis; HNC, head and neck cancers**

According to Spearman's correlation analysis, table 2 showed the association between the salivary IL-6 levels and the severity of OM based on the RTOG score. In the control group, the salivary IL-6 levels and OM severity demonstrated a moderate non-significant positive association with maximum significant rho value of 0.483 at week-5 of treatment, while the lowest non-significant association was reported at week-7. In the NS oil-treated group, significant positive association was reported throughout the first 5 w of treatment with maximum rho value reported at week5 (0.626,

$P=0.003$ ). Table 3 showed the association between the salivary TNF- $\alpha$  levels and the severity of OM. In the control group, the salivary TNF- $\alpha$  levels and the severity of OM (according to the RTOG scale) demonstrated a significant and positive association through the treatment weeks 4, 5 and 6 with maximum rho value reported at week 5 (0.735;  $P=0.0003$ ). In the NS oil-treated group, a weak significant association was reported only at week-4 of the treatment (rho=0.456;  $P=0.042$ ), while non-significant weak-moderate association was reported at the other time points of the treatment.

**Table 2: Correlation of salivary IL-6 level with the severity of oral mucositis assessed by the RTOG scale according to the type of treatment (NS oil mouthwash vs. magic mouthwash)**

Weeks	OM scale	Inflammatory marker	Control		NS Oil	
			rho value	P-value	rho value	P-value
One	RTOG	IL-6	0.195	0.41	0.556	0.011
Two	RTOG	IL-6	0.214	0.364	0.51	0.021
Three	RTOG	IL-6	0.22	0.349	0.543	0.013
Four	RTOG	IL-6	0.438	0.053	0.589	0.006
Five	RTOG	IL-6	0.483	0.03	0.626	0.003
Six	RTOG	IL-6	0.284	0.224	0.173	0.463
Seven	RTOG	IL-6	0.015	0.585	-0.291	0.358

Statistically analyzed using Spearman's Correlation. IL-6, interleukin-6; RTOG, radiation therapy oncology group; NS, *Nigella sativa*; OM, oral mucositis.

**Table 3: Correlation of salivary TNF- $\alpha$  level with the severity of oral mucositis assessed by the RTOG scale according to the type of treatment (NS oil mouthwash vs. Magic mouthwash)**

Weeks	OM scale	Inflammatory marker	Control		NS oil	
			rho value	P-value	rho value	P-value
One	RTOG	TNF- $\alpha$	0.187	0.56	0.193	0.413
Two	RTOG	TNF- $\alpha$	0.386	0.092	0.149	0.528
Three	RTOG	TNF- $\alpha$	0.365	0.113	0.456	0.042
Four	RTOG	TNF- $\alpha$	0.543	0.013	0.487	0.858
Five	RTOG	TNF- $\alpha$	0.735	0.0003	0.232	0.323
Six	RTOG	TNF- $\alpha$	0.498	0.025	0.181	0.445
Seven	RTOG	TNF- $\alpha$	0.408	0.147	0.511	0.089

Statistically analyzed using Spearman's Correlation. TNF- $\alpha$ , tumor necrosis factor-alpha; RTOG, radiation therapy oncology group; NS, *Nigella sativa*; OM, oral mucositis



## DISCUSSION

Oral mucositis is considered as the most intolerable adverse effect of RT or chemo-RT utilized for the treatment for HNC patients. It predisposes to ulceration, pain, dysphagia, weight loss and discontinuation of the treatment [15]. The present study indicated that exposure to ionizing radiation alone or in combination with chemotherapy caused OM in both NS oil and control groups; however, the use of NSoil can reduce the severity of intolerable OM in HNC patients undergoing RT or chemo-RT. Patients using the SN oil as a mouthwash had a significantly lower OM severity than those in the control group who are treated with a Magic mouthwash formula from weeks 3 to 7 of treatment. These results were in tune with many previously reported data about the efficacy of many natural compounds in the prevention and alleviation of RT or chemo-RT induced OM [16-18]. Many compounds have been tried to reduce or prevent RT-induced OM [19-21]; however, the clinical practice demonstrates various attitudes towards the use of an accepted medication for minimization and prevention of OM. Although palifermin was approved by the FDA in 2004 for the management of chemotherapy-induced OM in patients with hematologic malignancies, its use in RT-induced OM in HNC patients awaits for clinical evaluation [22, 23], in addition to the treatment cost burden and the safety concerns regarding the stimulation of tumor cell growth [24]. The NS oil mouthwash used in the present study is a natural product composed of many constituents that have been reported to possess many biological effects including anti-inflammatory activities. Although the pathophysiology of RT-induced OM is not yet completely verified, the secondary tissue injury attributed to excessive production of many pro-inflammatory cytokines including IL-6 and TNF- $\alpha$  are known to be involved in the disease process [25, 26]. Thymoquinone, one of the active ingredients of the NS oil has been shown to downregulate the expression of many proinflammatory cytokines in many preclinical studies [27].

Moreover, local application of NS oil is proved to be effective in the amelioration of experimentally-induced mouth ulceration in experimental animals [13]. Only few clinical data are reported involving salivary cytokines in patients with cancer-therapy induced OM [28, 29]. In the present study, salivary levels of IL-6 and TNF- $\alpha$  were significantly peaked on week-3 and week-5 respectively in both groups (control and NS oil), which coincide with the severity of OM and found to be compatible with the a previously reported data that demonstrate increased levels of these cytokines in association with the complications in patients during cancer treatment [30]. The present findings showed that the reduced levels of salivary IL-6 and THF- $\alpha$  after 3-5 w of treatment in the NS oil group may contribute to the reduction of local inflammation and consequently OM severity in HNC patients undergoing RT or chemo-RT. This seems compatible with a previous finding that indicates the association of OM severity with the elevation of salivary proinflammatory cytokines levels, including IL-6 and TNF- $\alpha$ , in patients receiving RT for HNC [25]. To our knowledge, this is the first pilot clinical study to evaluate the efficacy of NS oil mouthwash on RT or chemo-RT induced OM in HNC patients. However, there were few limitations in this study including the small sample size and the open-label approach of the study design. Therefore, the study lacks sufficient power to justify indisputable conclusions on the efficacy of NS oil mouthwash on RT or chemo-RT induced OM that should be confirmed by future studies. Additionally, due to unavailability of sufficient HNC patients, the inclusion of HNC patients receiving RT and chemo-RT in the present study may be one of the limitations since the mechanism of RT-induced OM differs from that induced by chemotherapy [31]; accordingly, it seems better to enroll only patients undergoing RT alone in this study for clear evaluation of the efficacy of this multi-component formula for treatment of RT-induced OM.

## CONCLUSION

This pilot clinical study showed that *Nigella sativa* oil mouthwash has a potential anti-inflammatory activity that may be beneficial in minimizing or preventing radiation-or chemoradiation-induced oral mucositis in patients with head and neck cancer.


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## AUTHORS CONTRIBUTIONS

All the author have contributed equally

## CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work, ORCID iD, Saad Abdulrahman Hussain  <http://orcid.org/0000-0002-1909-417X>

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